Nicotine: Actions on the Brain and Drug Interactions

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Prescription Drug Abuse- NIH 05-4881

- **Number of people in US abusing scripts (pain, benzo and ADHD meds) is only next to alcohol use and Marijuana**
- **60% of users receive them from friends or relatives**
- **17% obtained by "Doctor Shopping" with cc. pain**
- **4.3% from dealers----0.8% from internet**
- **Users recognize that prescription drugs less likely to be adulterated than street drugs**
- **OTC- Robotussin (Robotripping)- Doxylamine in Unisom, diphenhydramine, and dimenhydrinates in Dramamine**

Prescription Drug Abuse

- **4.7 Million used meds for nonmedical uses for the first time in 2002**
- **Three most frequent drugs are BZ, Opioids and Stimulants**
- **Persons 65 + are 13% of population but use 1/3 of all meds in US**
- **Use of prescription meds is more frequent than any illicit drug except marijuana**
- **OTC Meds can be abused**

DSM IVTR-Substance Abuse

- **Substance use with impairment with one of the following criteria in 12 months**

1. **Failure to fulfill major roles at work, school or home**
2. **Use in situations that are physically hazardous**
3. **Recurrent substance related legal problems**
4. **Continued use despite persistent or recurrent social or interpersonal problems**

Criteria of Any Addictive Disorder

- **DEPENDENCE not Abuse**
- **Loss of control (i.e. compulsive use)**
- **Continuation of behavior despite significant adverse consequences**
- **Preoccupation or obsession with obtaining, using and recovering from the effects of the drug (or behavior)**

Criteria for Dependence

Three or more sx required in 12 month period

1. **Tolerance (increased amounts needed for effect or diminished effect from the same dose)**
2. **Withdrawal (typical sx for the substance or another substance used to avoid sx**
3. **More use than intended**
4. **Desire to cut down or control use**
5. **Time used to obtain, use or recover from substance**
6. **Important activities given up or reduced**
7. **Continued use despite recurrent physical or psychological consequences**

General Addiction Issues

- **Not only the drug**
- **Genetic vulnerability**
- **Past developmental history- Conduct, ADHD, etc**
- **Environmental Factors- Stress etc**

How Addicting are different Substances

- **Probability of becoming dependent when you have tried a substance at least once**

Tobacco	32%
Heroin	23%
Cocaine	17%
Alcohol	15%
Stimulants	11%
Anxiolytics	9%
Cannabis	9%
Analgesics	8%
Inhalants	4%

Neurobiology

- **Our minds are programmed to pay extra attention to what neurologists call**
- **Salience-that is special relevance.**
- **Threats, for example, are highly salient, which is why we instinctively try to get away from them. So are food and sex because they help the individual and the species survive.**
- **Drugs of abuse capitalize on this ready-made programming.**
- **When exposed to drugs, our memory systems, reward circuits, decision-making skills and conditioning kick in**

Neurobiology continued

- **In the brains of addicts, there is reduced activity in the prefrontal cortex, where rational thought can override impulsive behavior**

- **Paulus found that 80% to 90% of the time, he could accurately predict who would relapse within a year simply by examining the scans.**

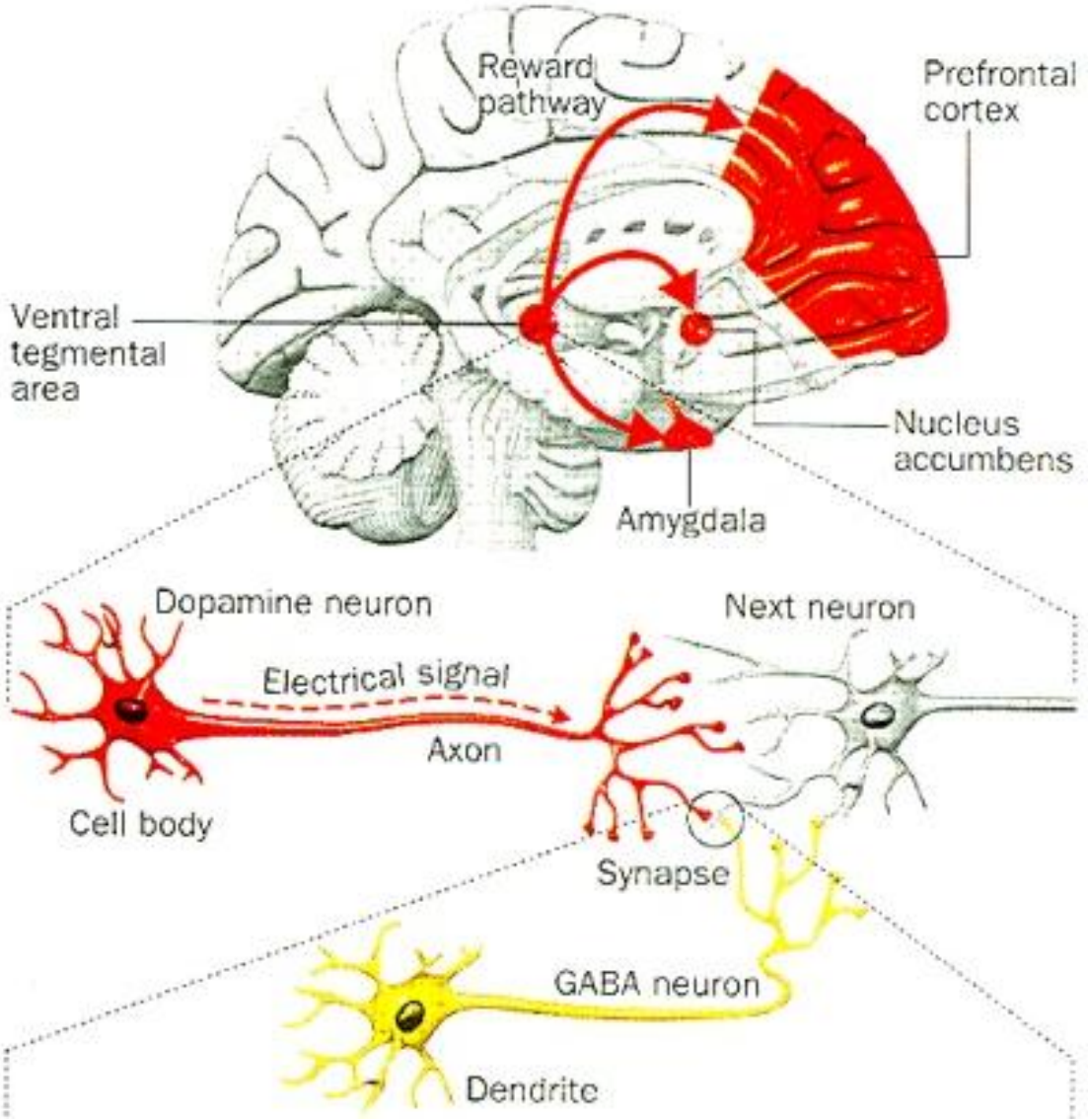
Reward Circuits

- **Mesolimbic Dopamine circuit- the final common path**
- **Dopamine- "pleasure neurotransmitter"**
- **"Natural Highs"- Drugs capitalize on this path**
- **Our Internal Pharmacy is very well supplied!**
  1. **Endorphins ----------Morphine**
  2. **Anandamide----------Marijuana**
  3. **Acetylcholine----------Nicotine**
  4. **Dopamine----------Cocaine/Methamphetamine**

What Happens in the Brain

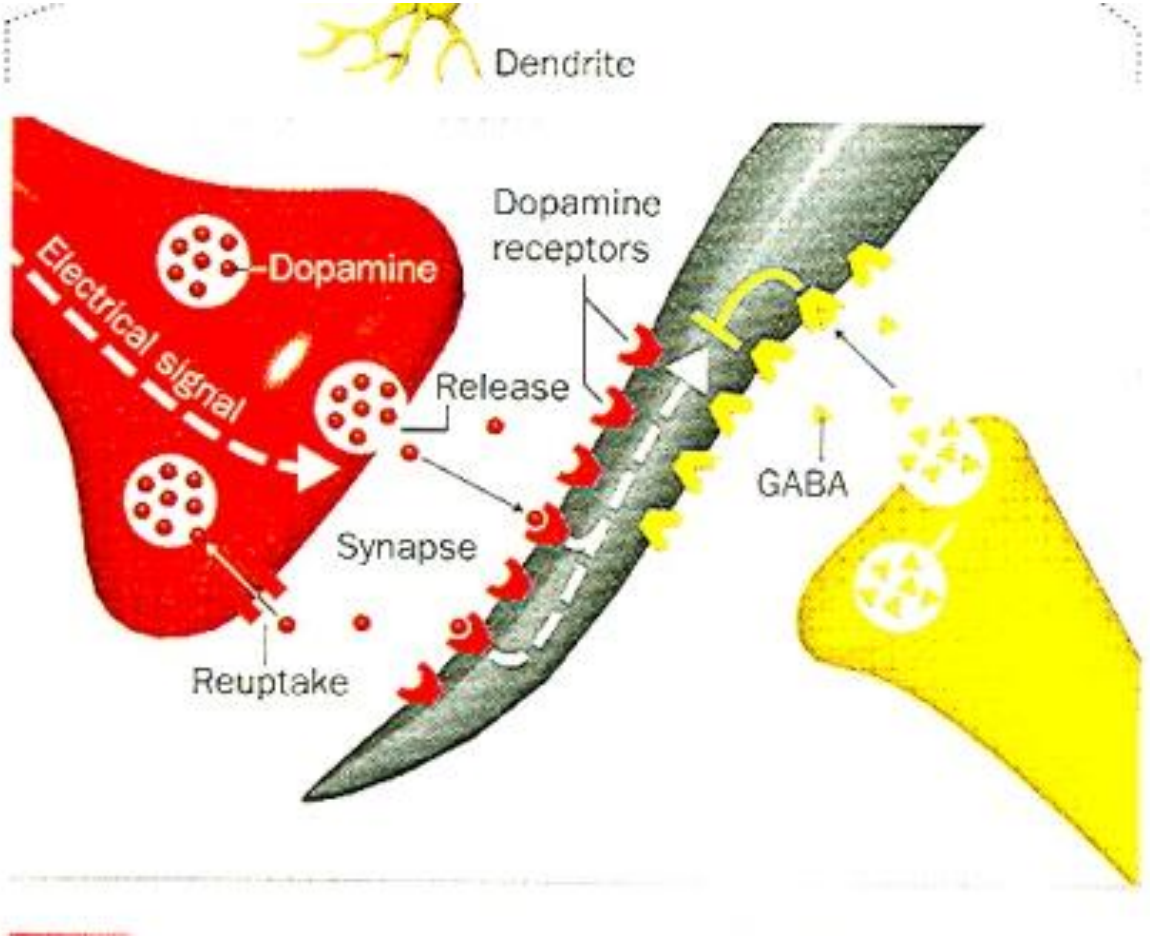
1. We feel good when neurons in the reward pathway release a neurotransmitter called dopamine into the nucleus accumbens and other brain areas.

2. Neurons in the reward pathway communicate by sending electrical signals down their axons. The signal is passed to the next neuron across a small gap called the synapse.



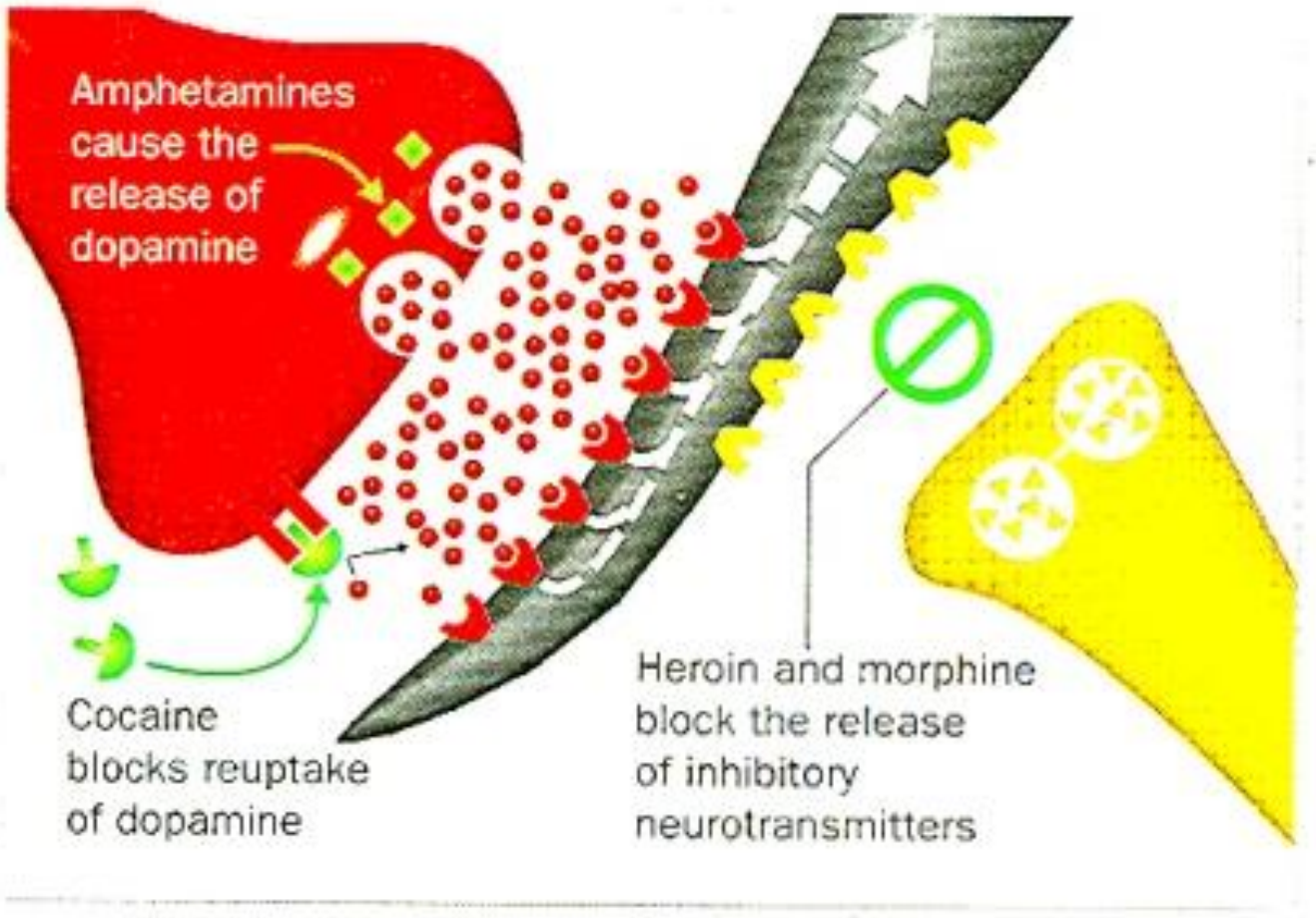
What Happens in the Brain

3. Dopamine is released into the synapse, crosses to the next neuron and binds to receptors, providing a jolt of pleasure. Excess dopamine is taken back up by the sending cell. Other nerve cells release GABA, an inhibitory neurotransmitter that works to prevent the receptor nerve from being overstimulated.



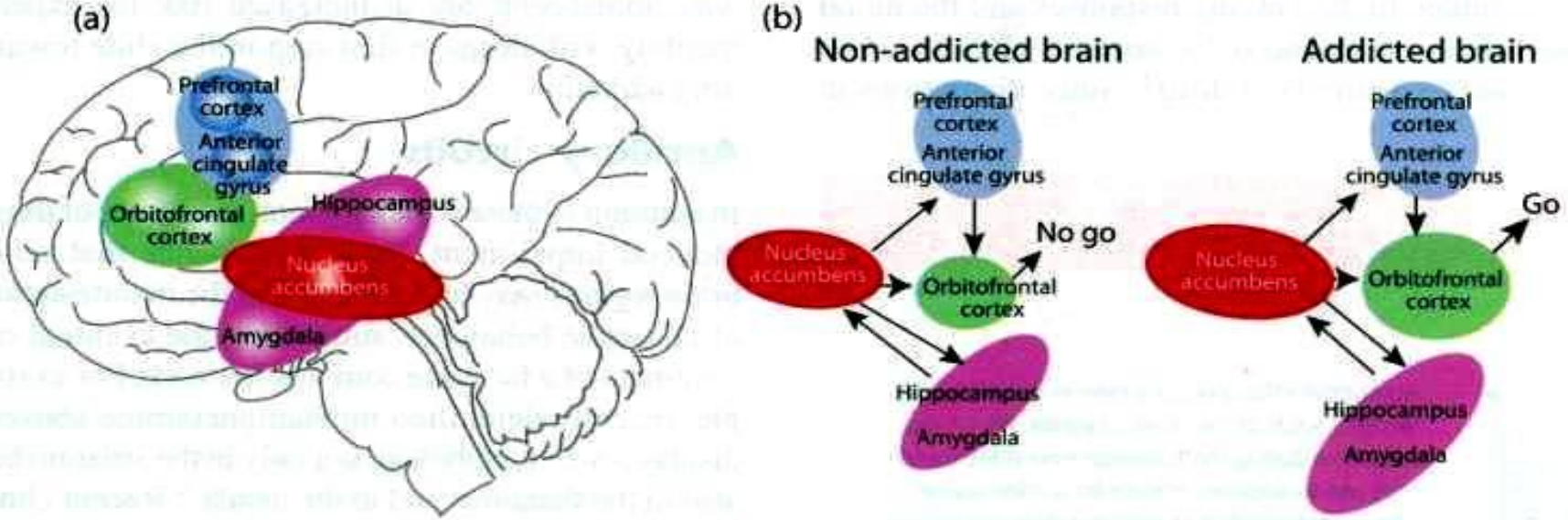
What Happens in the Brain

4. Addictive substances increase the amount of dopamine in the synapse, heightening the feeling of pleasure. Addiction occurs when repeated drug use disrupts the normal balance of brain circuits that control rewards, memory and cognition, ultimately leading to compulsive drug taking.



Addition Circuitry

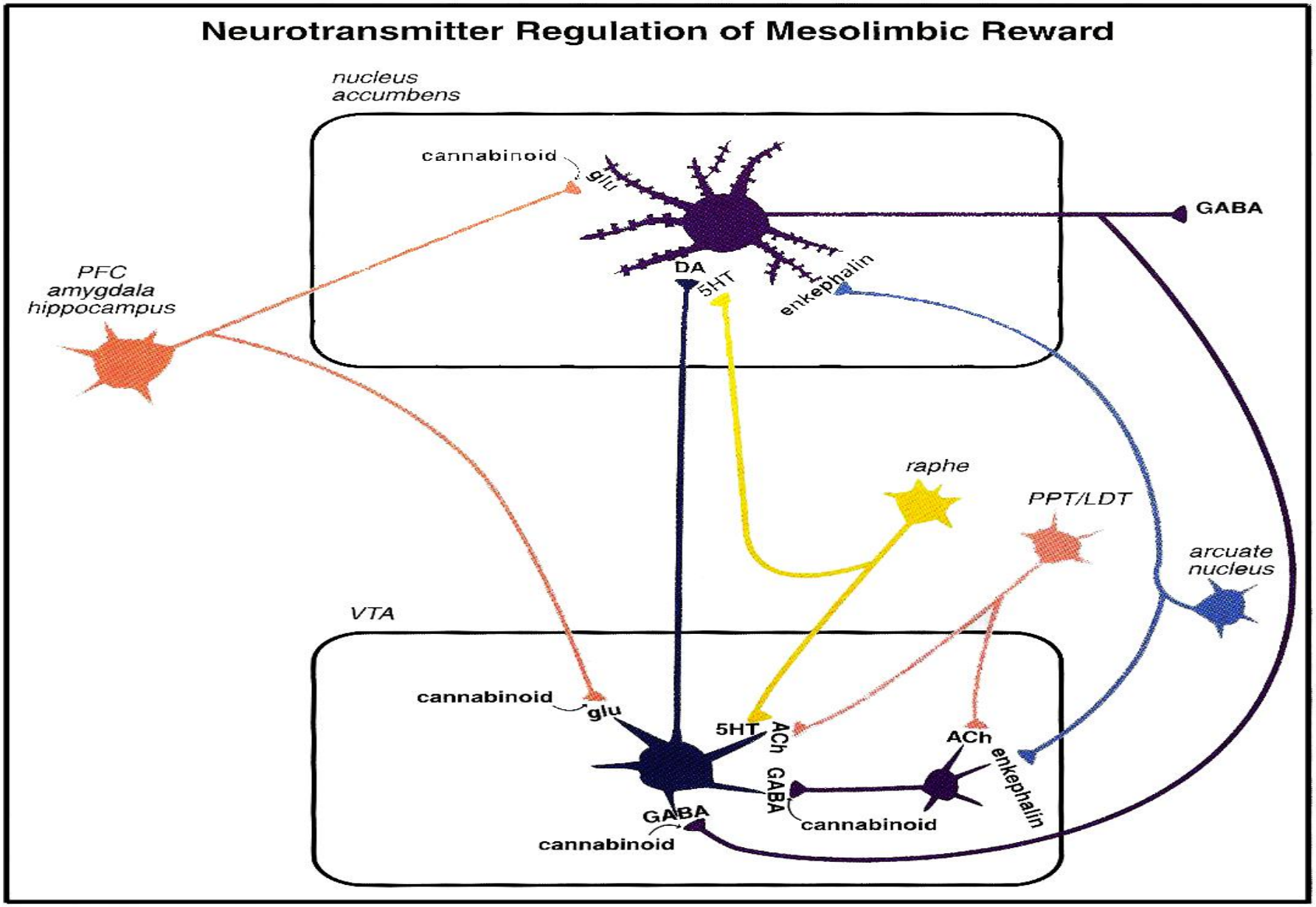
Figure 2 Addiction circuitry



(A) Schematic, sagittal view of a brain depicting 4 circuits that are postulated to have key interdependent and overlapping roles in addiction: (1) reward prediction and the core substrates of pleasure (red) located in the nucleus accumbens and ventral pallidum; (2) memory and learning, and the main substrate of conditioning (purple), located in the amygdala and hippocampus; (3) motivation, drive, and salience evaluation (green) located in the orbitofrontal cortex; and (4) cognitive control (blue), in charge of restraining cravings, located in the prefrontal cortex, and anterior cingulate gyrus. **(B)** Hypothetical model of addiction as the result of impaired information processing within the reward network. Compared with the nonaddicted state (left), the salience value of a drug (red), and its associated cues (purple), is enhanced in the addicted state (right), whereas the strength of inhibitory control is weakened (blue), setting the stage for an unrestrained motivation (green) resulting in compulsive drug taking without regard to potentially catastrophic consequences.

Dopamine- MANY FUNCTIONS

- **Neurotransmitter- Chemical Messenger**
- **Also Neurohormone released by Hypothalamus**
  (Inhibits release of Prolactin)
- **Medication- Acts on Sympathetic NS to increase heart rate and blood pressure**
- **Cannot cross Blood-Brain Barrier**
- **L-DOPA (precursor to DA) crosses BB barrier**
- **Low DA in Basal Ganglia causes Parkinson's**
- **CENTRAL TO REWARD SYSTEM OF BRAIN**
- **Dopamine antagonists are antipsychotics used to treat Schizophrenia (D1, D2, D3, D4, D5)**


Neurotransmitter Regulation of Mesolimbic Reward
nucleus accumbens
cannabinoid
glu
GABA
DA
5HT
enkephalin
PFC
amygdala
hippocampus
raphe
PPT/LDT
arcuate nucleus
VTA
cannabinoid
glu
5HT
ACh
ACh
enkephalin
GABA
cannabinoid
GABA
cannabinoid

Reactive Reward System

- **“BOTTOM UP” Demands- A drug-induced reward causes PS DA Receptors to crave more Dopamine**
- **Internal cues such as craving and withdrawal triggers drug seeking behavior**
- **Amygdala and Ventral Tegmental Areas influence higher cortical areas to provide for behavior and motivation to use more drug**
- **“Diabolical learning”- Theory by which changes in nearby synapses and circuits are recruited, healthy compensatory mechanisms are reduced and “sick” circuits become more efficient- A bad situation becomes worse!**

Dopamine and Diseases

- **High DA linked to Schizophrenia**
- **Amphetamine and cocaine increase DA levels**
- **Low DA levels associated with ADHD**
- **Mania associated with high DA**
- **Low DA associated with Parkinson's Disease**

Dopamine

- **Many drugs increase DA in the brain**
- **Food increases DA and leads to salient memory**
- **Sex increases DA**
- **Social Interactions increase DA**
- **BUT Drugs increase DA 5-10 times more than food or sex – METHAMPHETAMINE IS THE MOST POWERFUL DRUG INCREASING DOPAMINE**

Dopamine D2 Receptors

- **Reside in Mesencephalon then many projections**
- **ACTUALLY D2 RECEPTOR AVAILABILITY IS DECREASED IN DRUG ADDICTION (PROVEN IN COCAINE, ALCOHOL, HEROIN AND METH)**
- **Dopamine normally stays in receptor 50 milliseconds**
- **Addicts learn natural stimuli don't give much pleasure but drugs do**
- **In Cocaine/Meth use the Transporter is also blocked to prevent re-uptake of DA**

D2 Receptors in Animal Models

- **Rats trained to press lever to deliver shock to post-hypothalamus to give pleasure**
- **Current- if too low not reinforcing and too high is adversive**
- **Similar mechanism for addicts**
- **If low DA-RA person is vulnerable to drugs**
- **If high DA-RA person protected from drugs**
- **In Rats adenovirus can increase DA-RA by 50 %**
- **“Alcoholic” rats reduce alcohol intake by 70% when DA-RA is high- And alcohol intake increases when DA-RA is low------Same for Cocaine**

Reduced DA2 Receptor Availability

- **Is it present before addiction???????**
- **In Normals- 50% variation in DA-RA**
- **Experiment with 20 normals- With Ritalin about 50-50% said effect was either good or bad**
- **Pts with unpleasant reaction all had increased DA-RA**
- **Pts with pleasant reaction had low DA-RA which is the same for addicts**
- **THERE IS A UNIQUE INTERACTION BETWEEN THE DRUG AND THE PERSON'S BRAIN**
- **No way currently to increase DA-RA in humans**

How Can DA-RA be changed?

- **Genetically!**
- **Environment also- Dr Morgan- Monkey Studies-First raised in isolation then put in group**
- **Unable to predict which monkey would be Dominant or Subdominant based upon DA-RA**
- **HOWEVER DOM ANIMALS SHOWED INCREASE IN DA-RA BUT SUB DID NOT**
- **Increased level of DA-RA by social status**
- **Dominant animals would not self administer Cocaine but Subordinate animals did**

Dopamine Transporter

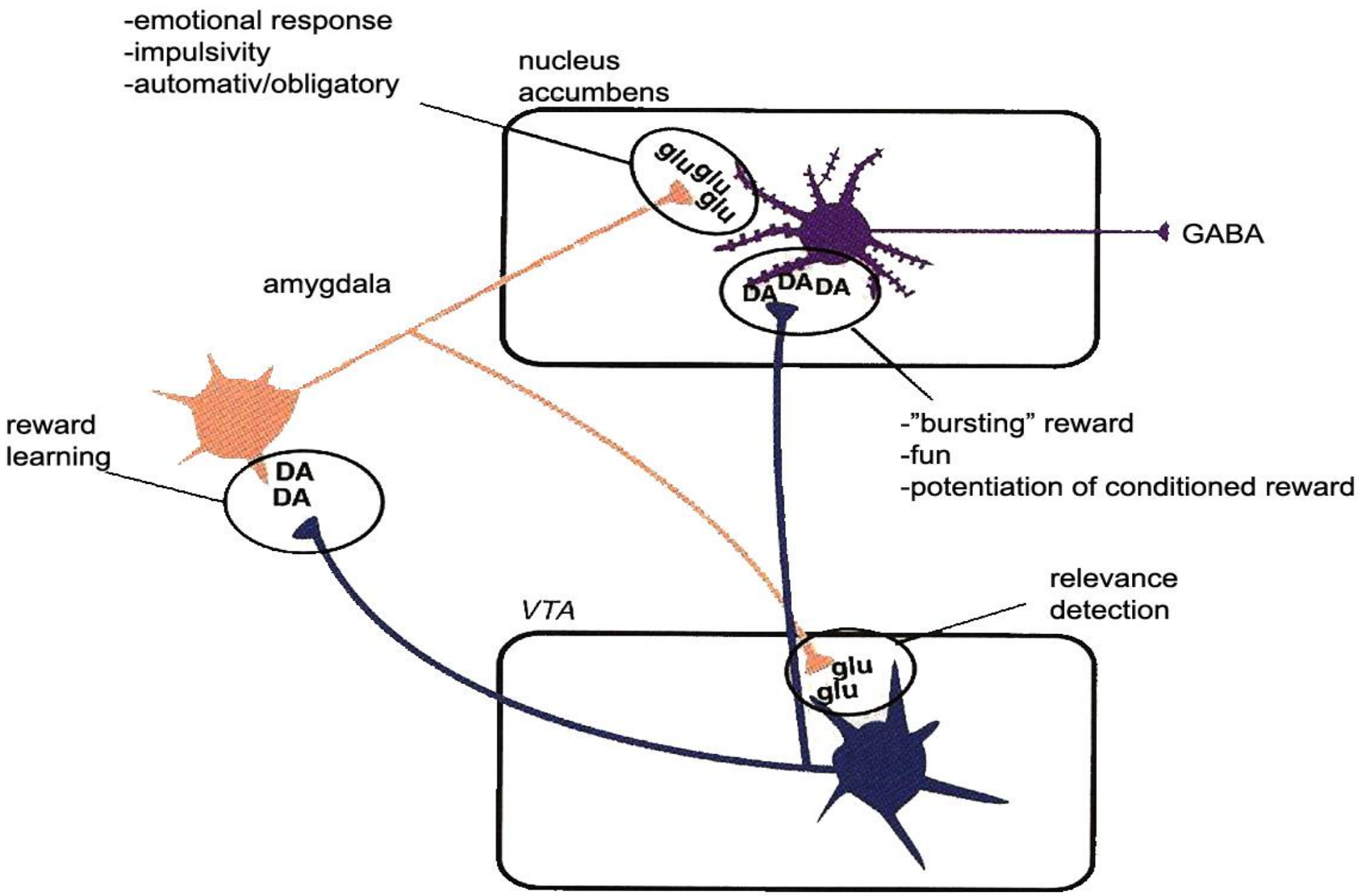
- **Meth users have much reduced levels**
- **The lower the level the worse on motor speed, fine motor tasks and memory**
- **Meth addicts had improvement in this after 9 months**
- **However glucose metabolism still deficient**
- **Even able to show reduction of the transporter in Nucleus Accumbens of addicts after 7 years**

Insula

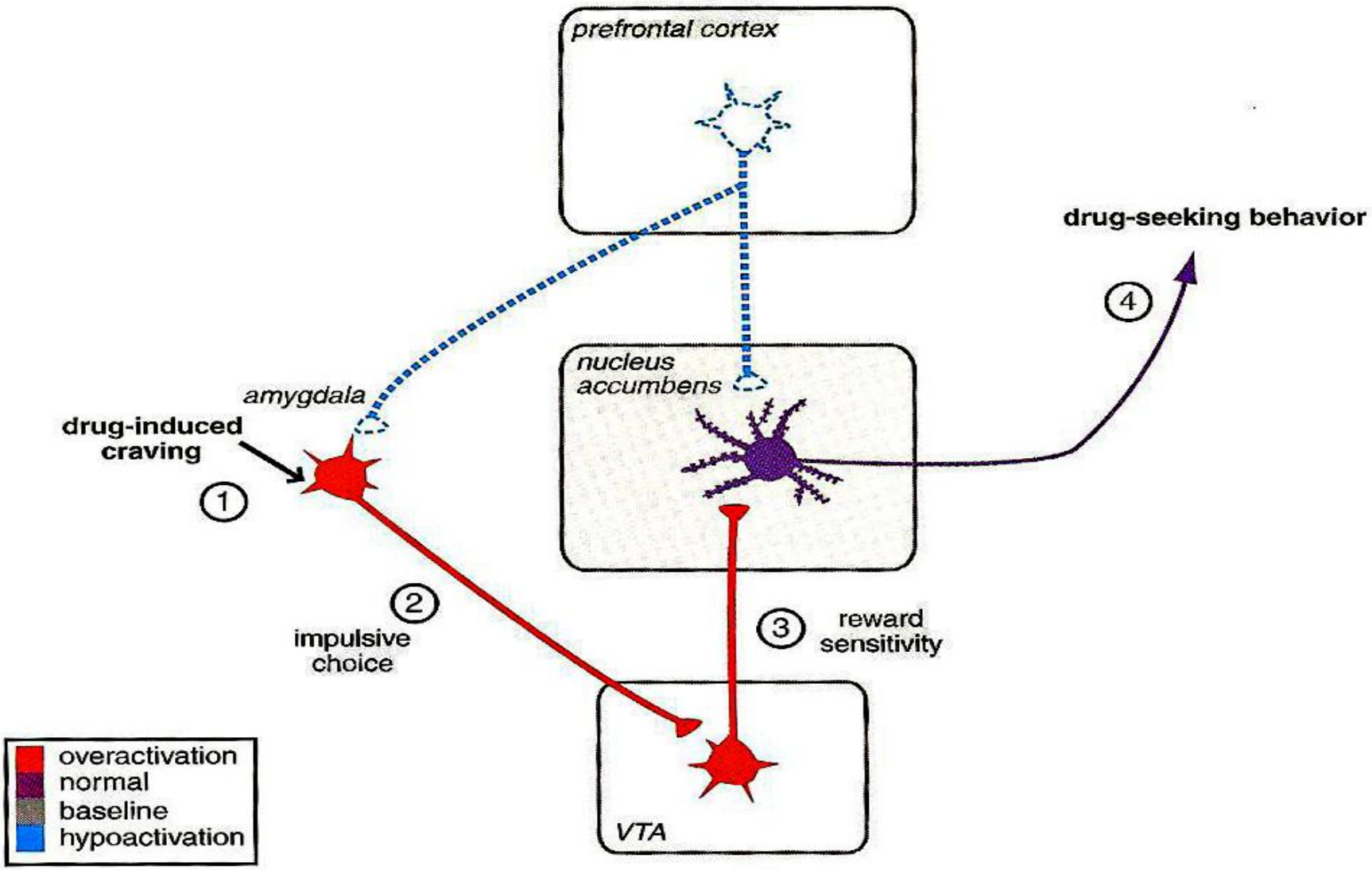
- **Region of the brain involved in emotional, gut-instinct perceptions**

- **Tobacco smokers with a stroke in this area no longer felt a desire for nicotine**

The Reactive Reward System

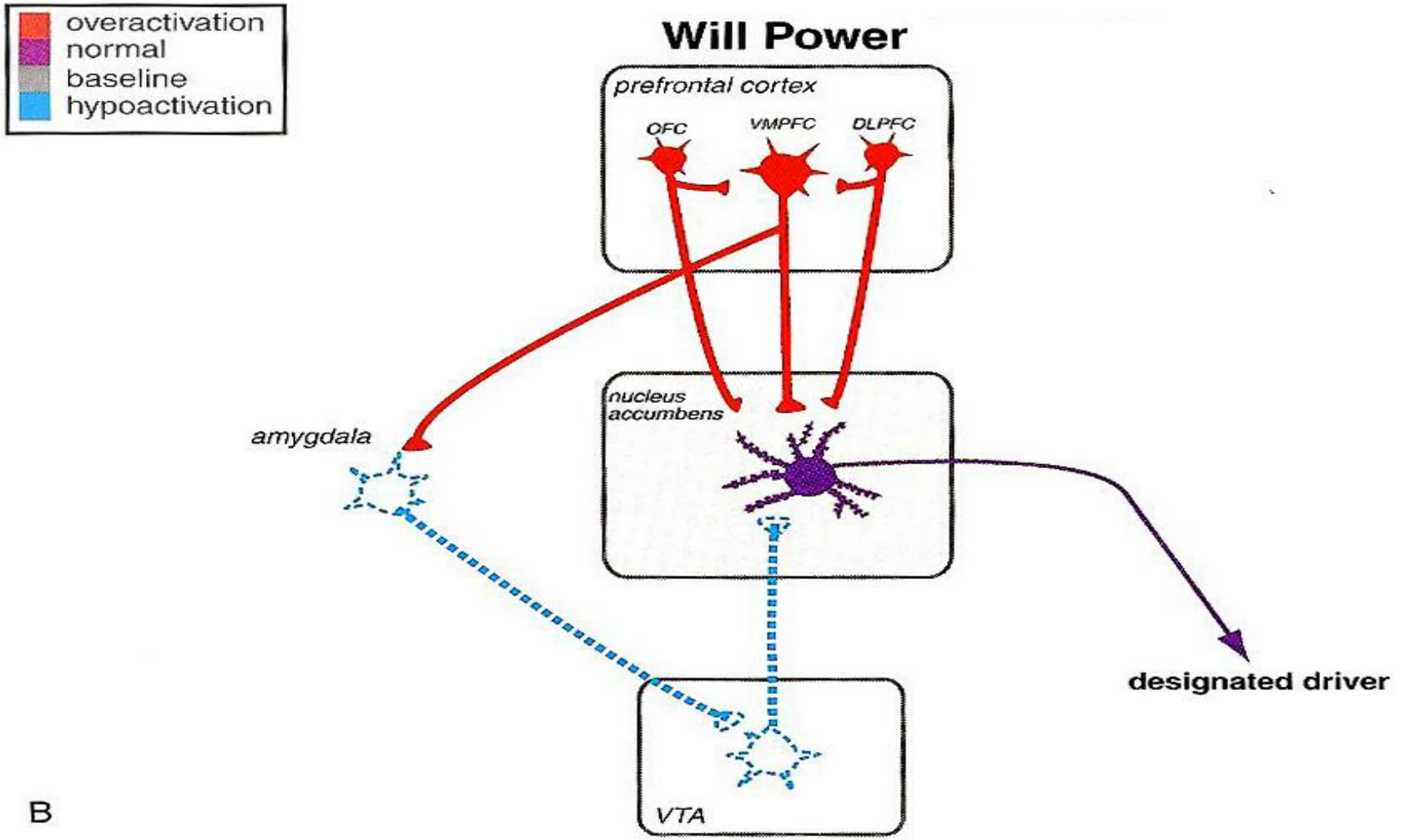


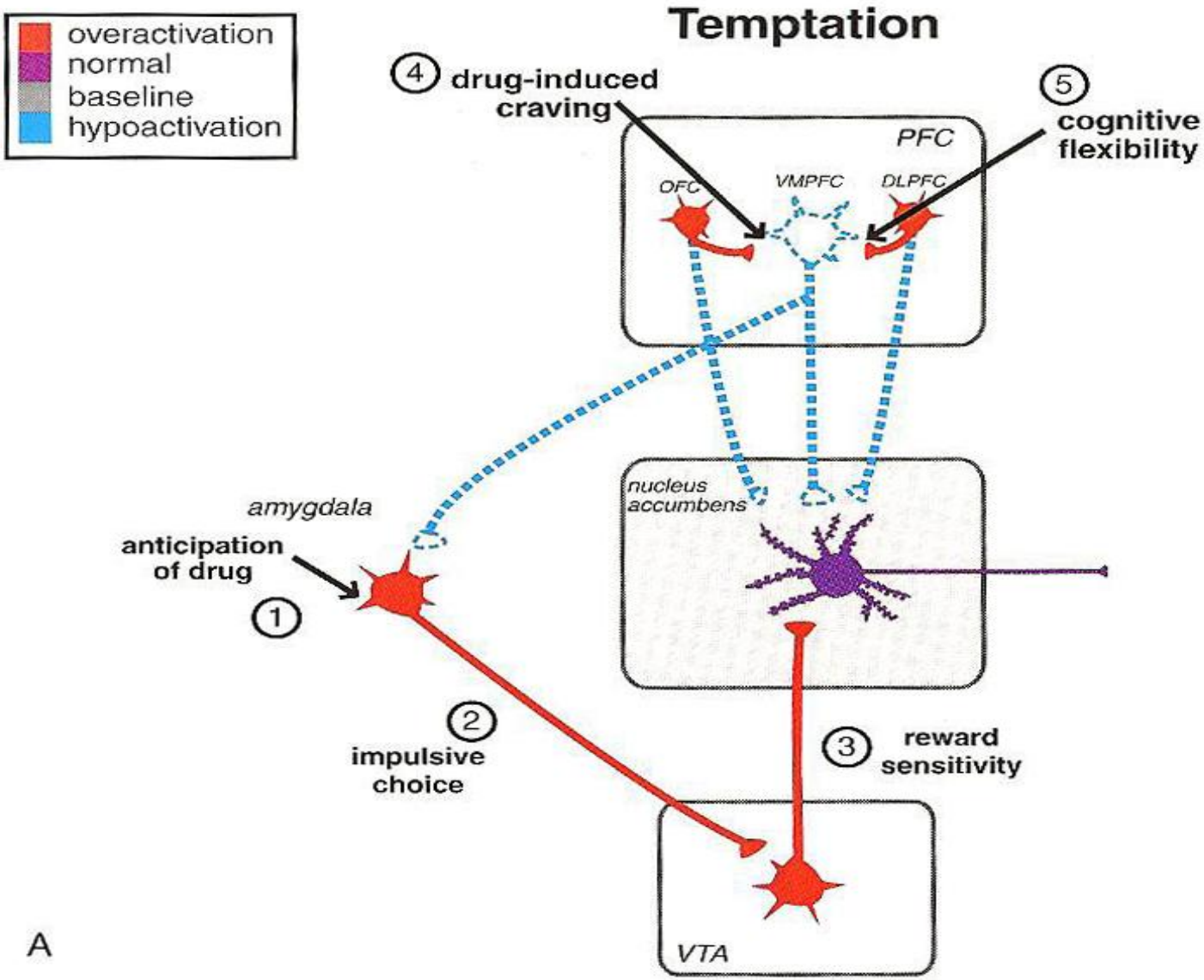
Compulsive Use/Addiction



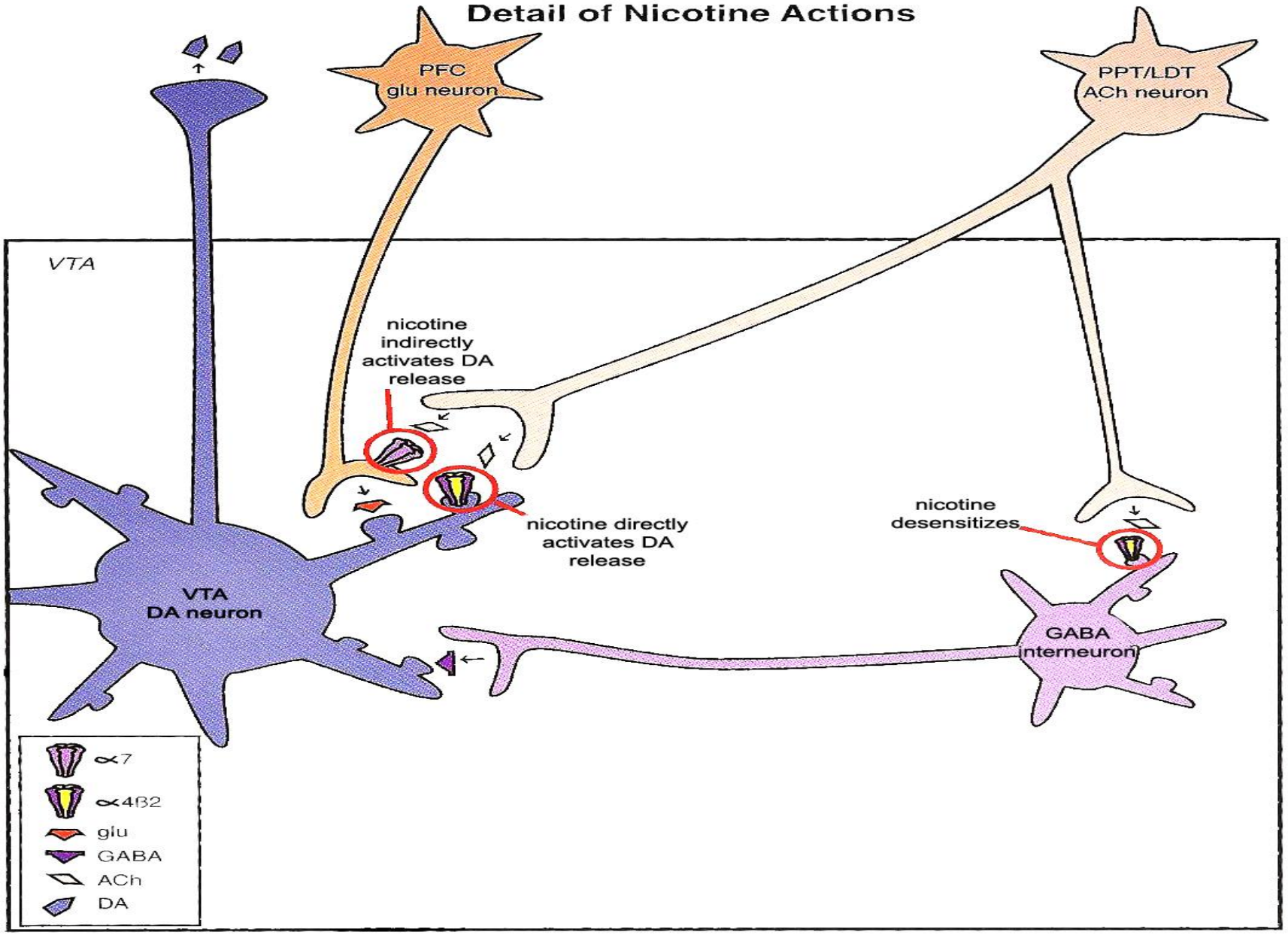
Reflective Reward System

- **Reward from the top down**
- **Prefrontal cortex down to the Nucleus Accumbens**
- **Regulation of emotions, analyzing situations and regulation of impulses**
- **Even the anticipation of the reward releases Dopamine**
- **Final output is to either stop the action that the reactive reward system is triggering or to let it happen**

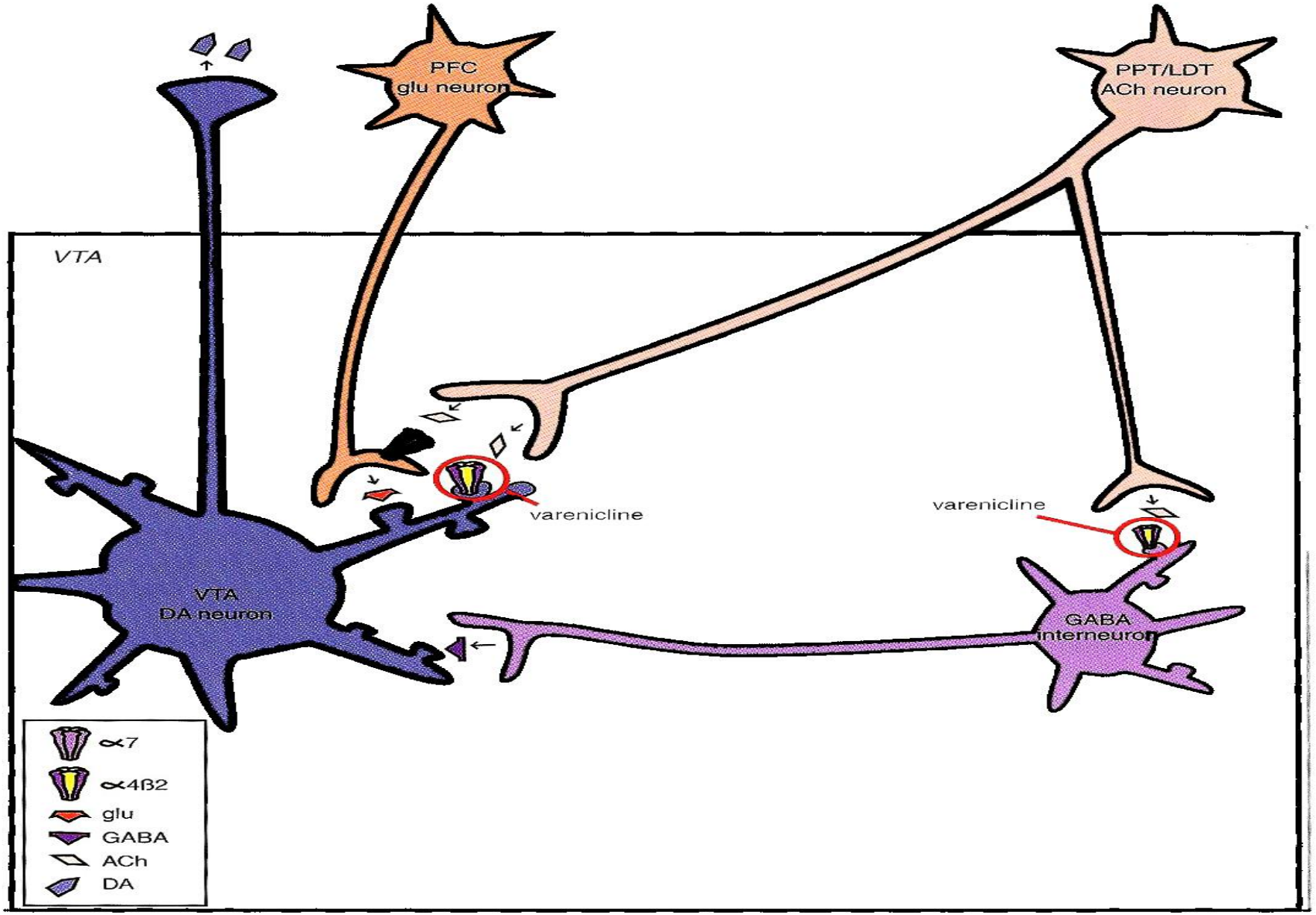

overactivation
normal
baseline
hypoactivation
Will Power
prefrontal cortex
OFC
VMPFC
DLPFC
nucleus accumbens
amygdala
designated driver
VTA
B

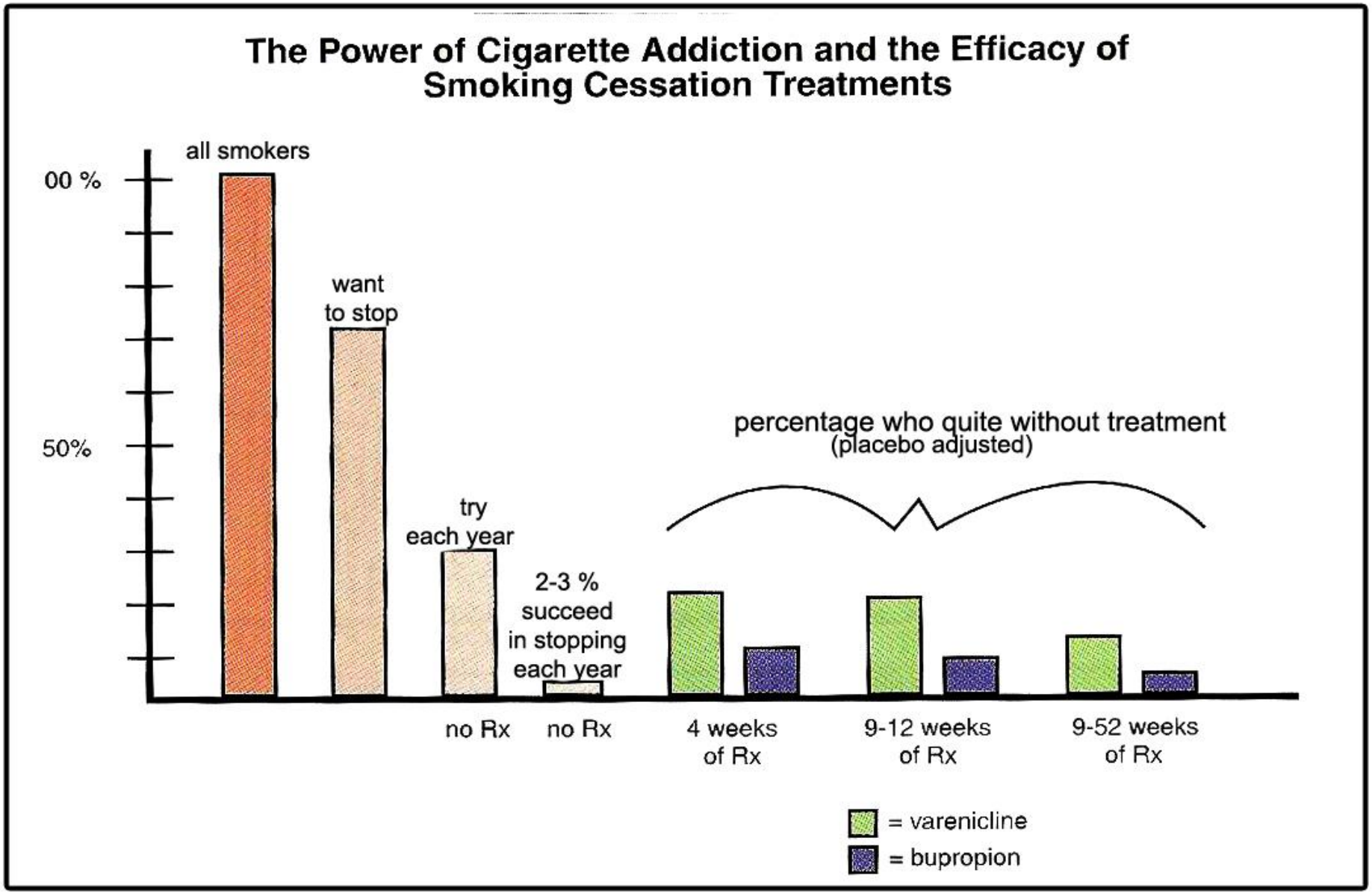

overactivation
normal
baseline
hypoactivation
Temptation
4 drug-induced craving
5 cognitive flexibility
PFC
OFC
VMPFC
DLPFC
nucleus accumbens
amygdala
anticipation of drug
1
2 impulsive choice
3 reward sensitivity
VTA
A

NICOTINE


Detail of Nicotine Actions
PFC
glu neuron
PPT/LDT
ACh neuron
VTA
nicotine
indirectly
activates DA
release
nicotine directly
activates DA
release
nicotine
desensitizes
VTA
DA neuron
GABA
interneuron
α7
α4β2
glu
GABA
ACh
DA

Varenicline Actions on Reward Circuits




The Power of Cigarette Addiction and the Efficacy of Smoking Cessation Treatments
all smokers
00 %
want to stop
50%
try each year
2-3 % succeed in stopping each year
percentage who quite without treatment (placebo adjusted)
no Rx
no Rx
4 weeks of Rx
9-12 weeks of Rx
9-52 weeks of Rx
= varenicline
= bupropion

Fagerstrom Test for Nicotine Dependence

1. **How soon after you wake up do you smoke your first cigarette? 60 minutes(0) 31-60 minutes(1) 6-30 minutes(2)Within 5 minutes(3)**
2. **Do you find it difficult to refrain from smoking in places where it is forbidden? No (0) Yes (1)**
3. **Which cigarette would you hate most to give up?**
   The first in the morning (1) Any other (0)
4. **How many cigarettes per day do you smoke?**
   10 or less (0) 11-20 (1) 21-30 (2) 31 or more (3)
5. **Do you smoke more frequently during the first hours after awakening than during the rest of the day?**
   No (0) Yes (1)
6. **Do you smoke even if you are so ill that you are in bed most of the day? No (0)Yes (1)**

0-2 Very low dependence **3-4 Low dependence**

6-7 High dependence **8-10 Very high dependence**

Pharmacological Treatments

- **Reduce signs/sx of drug intoxication or withdrawal**
- **Agonist substitution-change to less dangerous drug**
- **Abstinence &Relapse- Aversive use with drug/drug interaction-Antagonists to reduce drug reinforcing effects, etc**
- **Treat co-morbid psychiatric or medical conditions**

Table 4

Pharmacotherapy of Nicotine Withdrawal/Dependence

Bupropion: 150 mg q am x3 days, then 150 mg po bid; initiate 1 week before quit date and then treat for 7-12 weeks with up to 6 months for maintenance. Side effects include insomnia and dry mouth while contraindications include history of seizures, eating disorders, concurrent substance abuse withdrawal or use of monoamine oxidase inhibitors within 2 weeks.

Nicotine patch, gum, nasal spray, inhaler: Patch associated with better treatment adherence; gum can be given to patients with patch-induced rash; nasal spray gives patient rapid nicotine delivery while inhaler better simulates act of smoking.

Others: Clonidine and nortriptyline may be substituted when use of bupropion is not appropriate.

Source: Wilkins J (2005)

Table 4

Nicotine replacement and other options for smoking cessation

Drug	Daily dosage	Treatment duration*	Common side effects
Nicotine replacement therapy†			
Transdermal			Skin irritation, insomnia
24-hr patch	Starting dose is 21 mg/d; also in 7- and 14-mg patches for tapering dosage	8 wk	
16-hr patch	15 mg	8 wk	
Polacrilex (gum) 2- or 4-mg piece	1 piece/hr (<24 pieces/day)	8 to 12 wk	Mouth irritation, sore jaw, dyspepsia, hiccups
Vapor inhaler	6 to 16 cartridges/day (delivers 4/mg/cartridge)	3 to 6 mo	Mouth and throat irritation, cough
Nasal spray	1 to 2 doses/hr; dose = 1 mg (0.5 mg per nostril); maximum dosage 40 mg/d	3 to 6 mo	Nasal irritation, sneezing, cough, tearing eyes
Lozenge	2- or 4-mg dose; see dosage formula, titration schedule in over-the-counter package	12 wk	Hiccups, nausea, heartburn
Non-nicotine replacement therapy			
Sustained-release bupropion†	150 mg/d for 3 days, then 150 mg bid; start 1 week before quit date	7 to 12 wk; up to 6 mo. to maintain abstinence	Insomnia, dry mouth, agitation
Nortriptyline	75 to 100 mg/d; start 10 to 28 days before quit date at 25 mg/d and increase as tolerated	12 wk	Dry mouth, sedation, dizziness
Clonidine	0.1 to 0.3 mg bid	3 to 10 wk	Dry mouth, sedation, dizziness

* Treatment duration varies and may be longer in patients with psychiatric disorders.
† FDA-approved as a smoking cessation aid and recommended as a first-line drug by Public Health Service clinical guidelines
Source: Adapted from reference 21

Nicotine Replacement Therapy

- **5 FDA approved forms of NRT- patch, gum, lozenge, nasal spray and inhaler**
- **Choice depends upon patient preference**
- **Combination of NRT's, bupropion and psychosocial therapies may improve outcome**
- **Duration is debatable**
- **Dependence on NRT agents is rare**

Nicotine Patch Therapy

- **21 mg/day for 2 weeks, then 15mg/day for 2 weeks then 7.5 mg/day for 4 weeks**
- **24 hour patch (versus 16 hr) may relieve morning craving but may cause insomnia**
- **SE- skin irritation, nausea, vivid dreams**
- **Duration- 6-12 weeks- longer duration not found to be effective**

Nicotine Gum and Lozenges

- **Nicotine polacrilex- 2mg and 4mg**
- **2mg approved by FDA in 1984- 4mg in 1992**
- **Releases 50% N into the mouth thus 10-12 of 2mg gives 10mg/d or 20mg of 4mg**
- **This is 30-50% of 30 cigarettes/day**
- **Buffered with $NaCO_3$ and $NaBiCO_3$**
- **Absorption reduced by acids (coffee, coke)**
- **Cost- $40 for 104 tabs (either 2 or 4mg)**
- **Lozenge-SE nausea, heartburn, irritation**

Nicotine Nasal Spray/Inhalers

- **Spray- 0.5 to 1mg per pulse- higher doses quickly**

- **Inhaler gives 0.01mg after 35ml puff– cannot easily get higher doses- recommended dose 6-16 per day- 12 wks**

Bupropion-Zyban

- **Comparable tolerability/efficacy to NRT's**
- **Dose- 300mg/day**
- **Zyban much more expense than generic**
- **SE- headache, jitteriness, insomnia, GI**
- **Caution with pts with seizure history**
- **Seizures more common at 450md/day**

Chantix-Varenicline

- **Partial agonist selective for nicotinic receptors**
- **2 strengths- white 0.5mg and blue 1mg**
- **0.5 mg= 0.85 mg of varenicline**
- **Max plasma after 3-4 hr-steady in 4 days**
- **No drug-drug interaction- Rx for 12-24 weeks**
- **Dose-3 days 0.5mg/d, 4 days 0.5mg bid then 1mg bid----1 month pack then #56**
- **SE- nausea, sleep, constipation, flatulence**

Chantix- Continued

- **FDA warning in November, 2007**
- **Reports of depression, suicidal thoughts, aggressive and erratic behavior, and drowsiness**
- **FDA is conducting a safety review**

Other Agents

- **Nortriptyline**
- **Clonidine**
- **SSRI's**
- **Naltrexone**
- **Buspar**
- **Acupuncture**

New RX in Development

- **Vareniciline- partial agonist at nicotinic receptors-Mimics effects of N on DA release in Nucleus Accumbens but reduces later self-administration -5 studies completed- Approved by FDA in 2007**
- **Rimonabant- Cannabinoid CB1 receptor antagonist- reduces N use, DA turnover in NA- inhibits weight gain**
- **Vaccines- increase antibodies in blood that limits amt N in the brain and reduces DA in NA- well tolerated but short lived**

Drugs-Preclinical

- **DA D3 receptor blocking agents:**

  SB-277011-A, ST198, and BP 897

- **Dianicline- nicotinic partial agonist**

continued from page 82

Table 3

Smoking cessation may increase blood levels of these psychotropics

Antipsychotics	Antidepressants	Mood stabilizers	Anxiolytics
Haloperidol	Clomipramine	Carbamazepine	Desmethyldiazepam
Chlorpromazine	Desipramine		Oxazepam
Fluphenazine	Doxepin		
Olanzapine	Imipramine		
Clozapine	Nortriptyline		

Source: References 2, 5, and 20

Pharmacokinetic Mechanisms

- Drug interactions can occur via
- pharmacokinetic and pharmacodynamic mechanisms.
- Pharmacokinetic interactions are those that affect the
- absorption, distribution, metabolism, or elimination of
- other drugs, potentially causing an altered
- pharmacologic response.
- Polycyclic aromatic hydrocarbons (PAHs) are potent inducers of hepatic cytochrome P450 enzymes (CYP1A2)
- PAHs also induces increased glucuronide conjugation
- PAH causes these effects not nicotine by itself
- Most interactions are result of this induction

Pharmacodynamic Interactions

- Pharmacodynamic interactions alter the
- expected response or actions of other drugs. Such
- interactions may increase the risk of adverse events; for
- example in smokers with cardiovascular disease, and in
- women who smoke and use oral contraceptives.
- The nicotine in tobacco is highly addictive and can
- cause pharmacodynamic interactions.
- Nicotine activates the sympathetic NS and can counter actions of certain drugs

Pharmacodynamic Interactions Continued

- Polycyclic
- hydrocarbons and other tar-like compounds in
- tobacco smoke can increase the activity of several
- liver enzymes e.g. cytochrome P450 systems - primarily
- CYP1A2 but also CYP2A6, CYP2B6 and CYP2D6]),
- which are responsible for metabolising many different
- types of drugs. Enzyme induction results in faster
- clearance of medication from the body reducing
- serum drug levels and decreasing efficacy.

SMOKING AND HYPNOTICS AND ANXIOLYTICS

Drug/Class	Effects of Smoking	Effects of Smoking Cessation	Management of Smoking Cessation
Benzodiazepines e.g. Aprazolam Chlordiazepoxide Clonazepam Diazepam Loprazolam Lorazepam Lormetazepam Nitrazepam Oxazepam Temazepam	• Increased clearance due to enzyme induction leading to lowers plasma levels • Less sedation and drowsiness with high levels of nicotine • Possibly less hypnotic effect in smokers due to central nervous system (CNS) stimulation from nicotine • Smokers possibly need larger doses of some benzodiazepines than non-smokers	Plasma levels may rise due to reduced clearance of drug • Patients taking benzodiazepines may experience increased sedation after giving up smoking or on using therapies for smoking cessation	Monitor for increased sedation and hangover effects • Lower doses of benzodiazepines may be required

SMOKING AND HYPNOTICS AND ANXIOLYTICS

Drug/Class	Effects of Smoking	Effects of Smoking Cessation	Management of Smoking Cessation
Zolpidem	• Clearance is increased in smokers due to enzyme induction • Half life may be 30% shorter • Smoking may lower plasma levels • Possibly less hypnotic effect due to CNS stimulation from smoking • Heavy smokers may require higher doses of zolpidem	• Clearance of zolpidem is reduced and plasma levels increase • Sedation may increase	Dose reduction may need to be considered especially if there are symptoms of increased sedation and substantial hangover effects

SMOKING AND DRUGS USED IN PSYCHOSES AND RELATED DISORDERS

Drug/Class	Effects of Smoking	Effects of Smoking Cessation	Management of Smoking Cessation
Antipsychotics - general	• Smoking reduces the blood levels of some antipsychotics via increased metabolism • Smokers may need higher doses • Smoking may increase some antipsychotic side effects	• Serum levels increase due to reduced clearance • Lower doses of antipsychotics may be required on stopping smoking or using therapies for smoking cessation	• Monitor response • If more sedated or increased side effects, such as hypotension, drowsiness or extrapyramidal side effects [EPSE], then reduce dose

SMOKING AND DRUGS USED IN PSYCHOSES AND RELATED DISORDERS

Drug/Class	Effects of Smoking	Effects of Smoking Cessation	Management of Smoking Cessation
Chlorpromazine (phenothiazines)	• Serum levels may be lower in smokers due to increased clearance but clinical significance unclear • Less drowsiness and hypotension in smokers	• Serum levels increase due to reduced clearance • May need lower doses on stopping smoking or using therapies for smoking cessation	• Consider dose reduction if side effects such as drowsiness or EPSEs increase • Lower doses may be required

SMOKING AND DRUGS USED IN PSYCHOSES AND RELATED DISORDERS

Drug/Class	Effects of Smoking	Effects of Smoking Cessation	Management of Smoking Cessation
Clozapine	• Serum levels are lower in smokers because smoking induces clozapine metabolism • Smokers may need higher doses	• Plasma clozapine concentrations increase significantly on stopping smoking or using therapies for smoking cessation • Risk of adverse effects increases	• Monitor side effects • Measure levels before quitting and 2 weeks after; earlier if side effects occur • Significantly lower doses may be required

SMOKING AND DRUGS USED IN PSYCHOSES AND RELATED DISORDERS

Drug/Class	Effects of Smoking	Effects of Smoking Cessation	Management of Smoking Cessation
Haloperidol	• Serum levels may be around 20% lower in smokers due to increased drug clearance as a result of induction of drugmetabolising enzymes • Smokers require higher doses	• Serum levels increase due to reduced metabolism • Side effects may increase • Patients taking haloperidol may require lower doses after stopping smoking	• Monitor symptoms • Consider dose reduction if adverse effects such as drowsiness, hypotension or EPSEs increase

SMOKING AND DRUGS USED IN PSYCHOSES AND RELATED DISORDERS

Drug/Class	Effects of Smoking	Effects of Smoking Cessation	Management of Smoking Cessation
Olanzapine	• Smoking increases the clearance of olanzapine as a result of induction of drug-metabolising enzymes • Half life may be around 20% shorter in smokers • Serum levels lower in smokers	• Serum olanzapine levels increase significantly on stopping smoking due to reduced clearance caused by a slower metabolism	• Monitor closely • Lower doses of olanzapine may be required • Consider dose reduction if adverse effects e.g. drowsiness, hypotension occur

SMOKING AND DRUGS USED IN PSYCHOSES AND RELATED DISORDERS

Drug/Class	Effects of Smoking	Effects of Smoking Cessation	Management of Smoking Cessation
Aripiprazole **Quetiapine** **Risperidone** **Ziprasidone**	• Smoking appears to have no effect on serum levels	• No known clinically significant effects	• Monitor

SMOKING AND ANTIDEPRESSANT DRUGS

Drug/Class	Effects of Smoking	Effects of Smoking Cessation	Management of Smoking Cessation
SSRIs fluvoxamine	• Smoking may alter drug clearance of fluvoxamine as a result of enzyme induction • Serum levels are significantly lower in smokers than nonsmokers	• Serum levels may increase on stopping smoking or using therapies for smoking cessation	• Monitor for side effects and consider dose adjustment, if appropriate

SMOKING AND ANTIDEPRESSANT DRUGS

Drug/Class	Effects of Smoking	Effects of Smoking Cessation	Management of Smoking Cessation
Tricyclics e.g. amitriptyline clomipramine imipramine nortriptyline,	• Smoking reduces the plasma levels of tricyclics • Cigarette smoke may increase drug clearance due to induction of hepatic drug-metabolising enzymes • Although serum levels of tricyclic antidepressants fall in smokers, free drug levels rise, minimising the clinical significance	• Serum levels may increase on stopping smoking or using therapies for smoking cessation	• Monitor for side effects and consider dose adjustment, if appropriate

SMOKING AND ANTIDEPRESSANT DRUGS

Drug/Class	Effects of Smoking	Effects of Smoking Cessation	Management of Smoking Cessation
Duloxetine	• Smokers may have plasma levels 50% lower than nonsmokers due to enzyme induction and increased metabolism	• Serum levels may increase on stopping smoking or using therapies for smoking cessation	• Monitor for increased side effects • Dose reduction may be required

SMOKING AND DRUGS FOR DEMENTIA

Drug/Class	Effects of Smoking	Effects of Smoking Cessation	Management of Smoking Cessation
Acety-Icholinesterase Inhibitors Donepezil-Aricept Galantamine Rivastigmine	• Smoking not thought to have any clinically significant influence on plasma levels of Acety-Icholinesterase inhibitors • Major enzyme systems minimally involved in metabolism – effect not clinically significant	• No known clinically significant effects	• Monitor

SMOKING AND MOOD STABILISERS

Drug/Class	Effects of Smoking	Effects of Smoking Cessation	Management of Smoking Cessation
Anticonvulsants e.g. carbamazepine, valproate	• Smoking appears to have no important effect on the serum levels • A minor fraction of these drugs is metabolized by enzymes.	• No known clinically significant effects	• Monitor

SMOKING AND MOOD STABILISERS

Drug/Class	Effects of Smoking	Effects of Smoking Cessation	Management of Smoking Cessation
Lithium	• Indirect drug-diet interaction • Smoking increases caffeine metabolism via enzyme induction • Significant changes in amount of caffeine may affect serum lithium levels	• Theoretically , ceasing smoking could indirectly alter lithium excretion	• Check levels especially if deterioration evident

SMOKING AND NON-PSYCHOTROPIC DRUGS

Drug/Class	Effects of Smoking	Effects of Smoking Cessation	Management of Smoking Cessation
Analgesics Dextro-propoxyphene-Darvon Codeine **Anti-inflammatory** Diflunisal- Dolobid Phenylbutazone	• Dextro-propoxyphene and pentazocine are less effective as analgesics in smokers than in nonsmokers • The clearance of diflunisal and phenylbutazone from the body is greater in smokers than in non-smokers.	• Improved response to analgesic	• Monitor response

SMOKING AND NON-PSYCHOTROPIC DRUGS

Drug/Class	Effects of Smoking	Effects of Smoking Cessation	Management of Smoking Cessation
Beta-Blockers	• Smoking can reduce the beneficial effect of beta-blockers on blood pressure and heart rate. • Smokers may need larger doses due to increased clearance	• Effects of beta blockers may be enhanced by quitting smoking • Lower doses may be required on stopping smoking	• Monitor blood pressure/pulse • If a person taking beta-blockers stops smoking, the dose may need to be reduced.

SMOKING AND NON-PSYCHOTROPIC DRUGS

Drug/Class	Effects of Smoking	Effects of Smoking Cessation	Management of Smoking Cessation
Histamine$_2$ Blockers Cimetidine-Tagamet Ranitidine Famotidine-Pepcid	• Smoking may reduce the plasma levels of cimetidine and ranitidine, but does not appear to affect famotidine • Cimetidine, and to a lesser extent ranitidine, reduce the clearance of nicotine from the body in non-smokers	• Improved response to H2 blocker expected	• Monitor response

SMOKING AND NON-PSYCHOTROPIC DRUGS

Drug/Class	Effects of Smoking	Effects of Smoking Cessation	Management of Smoking Cessation
Insulin	• Smoking decreases the absorption of insulin and may increase insulin resistance • Smokers who have insulin-dependent diabetes may need more insulin than non-smokers	• Quitting improves glycaemic control • Insulin requirement may be reduced • Dose may need to be adjusted according to individual need	• Monitor for hypoglycaemia • Check blood glucose more frequently • Insulin-dependent diabetics may need less insulin

SMOKING AND NON-PSYCHOTROPIC DRUGS

Drug/Class	Effects of Smoking	Effects of Smoking Cessation	Management of Smoking Cessation
Theophylline/ Aminophylline	• Smoking increases theophylline clearance • In smokers, the half-life of theophylline is reduced, clearance is considerably more rapid, due to enzyme induction • Smokers need higher doses than nonsmokers. For heavy smokers the dose may need to be doubled.	• The plasma concentration of theophylline will increase significantly when smoking stopped • Theophylline has a narrow therapeutic range – so toxicity is possible	• Monitor for signs of toxicity e.g palpitations or nausea. • The dose will need to be reduced • Plasma levels should be checked and dose adjusted accordingly [typically needs reduction by about a third]

SMOKING AND NON-PSYCHOTROPIC DRUGS

Drug/Class	Effects of Smoking	Effects of Smoking Cessation	Management of Smoking Cessation
Anticoagulants Warfarin Heparin	• Smoking may slightly increase warfarin metabolism and clearance slightly reducing response to warfarin • Reduced half-life and increased elimination of heparin have been reported in smokers • Smokers may possibly need higher doses to achieve anticoagulation.	• Dose requirements may be slightly increased. • International Normalised ratio [INR] /Prothromin time may increase.	• Monitor closely • The dose of anticoagulant should be adjusted according to each patient's International Normalised Ratio (INR) / Prothrombin time

SMOKING AND NON-PSYCHOTROPIC DRUGS

Drug/Class	Effects of Smoking	Effects of Smoking Cessation	Management of Smoking Cessation
Caffeine	• Increased metabolism • Induction of CYP1A2 increased clearance 56%	• Increased caffeine levels	• Monitor Reduce Caffeine by 50% Caffeine toxicity may be masked by nicotine withdrawal

SMOKING AND NON-PSYCHOTROPIC DRUGS

Drug/Class	Effects of Smoking	Effects of Smoking Cessation	Management of Smoking Cessation
Hormonal Contraceptives	• Increased risk of cardiovascular effects • Increased risk with age	• No known clinically significant effects	• Monitor

Future trends

- **Negative-**
- **1. Increase in potency of Marijuana**
- **2. Prescription drug use continued increase**
- **Positive-**
- **1. Neurobiology advances**
- **2. New meds to treat addictions**
- **3. Clinical and genetic biomarkers**
- **4. Vaccines to treat nicotine, cocaine, meth, heroin**
- **5. Monoclonal antibodies to treat OD's**
- **6. Meds to target extinction/unlearning**
- **7. Better ID's of vulnerable/ high risk groups**